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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE APPLN. OF: TAPER et al.

SERIAL NO.: 09/700,573

FILED: November 16, 2000

FOR: SYNERGISTIC COMPOSITION FOR USE IN THE TREATMENT...

GROUP: 1614

EXAMINER: ZOHREH A. FAY DOCKET: TIENSE RAFF.28

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Dear Sir:

In response to the communication mailed July 15, 2005, Appellants hereby submit a corrected Brief. The Examiner has rejected the Brief, as same did not contain the items under 37 CFR 1.192(c). Appellants note that all sections are present but that the "Status of the Claims" and the "Status of the Amendments" sections were in a different order. Appellants have made the appropriate change and hereby resubmit the Brief, along with copies of the evidence Appendices, which were already submitted with the original Brief.

Appellants believe there are no fees associated with this replacement Brief.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: MAIL STOP APPEAL BRIEF - PATENTS, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on August 10, 2005 at Tucson, Arizona.

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APPELLANTS' SUBSTITUTE BRIEF ON APPEAL

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TABLE OF CASES

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APPELLANTS' SUBSTITUTE BRIEF ON APPEAL

This Brief is being filed in support of Appellants' Appeal from the Final Rejection by the Primary Examiner to the Board of Appeals and Interferences. A Notice of Appeal is being timely filed contemporaneously herewith.

REAL PARTY IN INTEREST

The Real Party in Interest in this Appeal is Tiense Suikerraffinaderij N.V., a Belgian corporation having its principal place of business at Tervurenlaan 182, B - 1150 Bruxelles, Belgium. The Application has been assigned to Tiense Suikerraffinaderij N.V. by the inventors Henryk Taper, Anne Frippiat, Jan Van Loo and Marcel Roberfroid, and the Assignment recorded in the U.S. Patent and Trademark Office on November 16, 2000 at Reel 011434, Frame 0666.

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RELATED APPEALS AND INTERFERENCES

To the best of the knowledge of the undersigned attorney and the Appellants, there are no other appeals or interferences that would directly affect, or be directly affected by, or have a bearing on, the Board's decision in the present Appeal.

STATUS OF THE CLAIMS ON APPEAL

Claims 21-33 and 35-40 stand finally rejected and are on Appeal. The claims on Appeal are set forth in **Appendix A** attached hereto.

STATUS OF THE AMENDMENTS

The last amendment entered in this case, Amendment D, was in response to an earlier rejection (Office Action mailed May 17, 2004). Appellants chose not to respond to the outstanding Final Rejection since it was the second rejection on the same issues (37 CFR 1.191(a)).

SUMMARY OF THE INVENTION ON APPEAL

Cancer is a major cause of death in humans, particularly in developed and industrialized nations. Various methods for treatment of cancer have been developed, including surgery, chemotherapy, irradiation, and frequently, combinations of two or more of the above.

While surgical and irradiation treatments have been fine-tuned, the most significant improvements in cancer treatment and the greatest opportunity for improvement is in the chemotherapy area. Various anti-cancer drugs have been developed, most of which have serious side effects and disadvantages. These include a high degree of toxicity for healthy cells, increased sensitivity to opportunistic infections, and various types of discomfort for the treated person including, for example, local necrosis of the body structure in which the drug is

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administered, nausea, vomiting, irritation of the mucoses of the digestive tract, diarrhea, megaloblastose, and lesions of the liver or digestive tract, such as stomatitis and buccal and gastro-intestinal ulcers. (Specification, page 2, line 29 -- page 3, line 2).

Such side effects and disadvantages considerably limit the use of available anti-cancer drugs. Indeed, often a curative effective dose of a cancer drug cannot be given to a patient due to the high toxicity of the drug to normal cells or to the high degree of discomfort caused to the patient by the drug. (Specification, page 3, line 3 -- line 7).

The present invention overcomes the aforesaid and other problems of conventional anti-cancer chemotherapy by providing a novel pharmaceutical composition comprising a combination of inulin and an anti-metabolic anti-cancer drug, which combination unexpectedly provides a synergistic therapeutic effect on the carcinogenesis and growth of cancer. (Specification page 7, line 16 -- line 25).

Inulin is a non-digestible carbohydrate. More particularly, inulins are D-fructans consisting of water-soluble chains of fructose units. Inulin mostly occurs as a polydisperse mixture of linear polyfructose molecules as, for example, inulin from chicory, but inulin also can occur as a polydisperse mixture of branched polyfructose molecules as, for example, inulin from dahlia and inulin from agave. (Specification, page 4, line 3 -- line 10).

In view of their almost non-digestibility by alimentary enzymes of humans and non-ruminating mammals, inulins are generally considered to be dietary fibers or non-digestible carbohydrates. (Specification, page 5, line 36 -- page 6, line 2).

The present invention is based on the discovery that a combination of inulin and an anti-metabolic anti-cancer drug unexpectedly provokes a synergistic therapeutic effect on the carcinogenesis and growth of cancer in humans and in non-ruminating mammals. That is to

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say, the present invention is based on the discovery that inulin, a non-digestible carbohydrate, when administered together with an anti-metabolic anti-cancer drug, provides a synergistic anti-cancer effect to a human or non-ruminating mammal undergoing treatment for cancer. (Specification page 7, line 16 -- line 25). As demonstrated in the working examples in the Specification, this synergistic effect is and is unique to a combination of inulin and an anti-metabolic anti-cancer drug, as the effect of combined treatment of inulin and other classes of anti-cancer drugs were found to be only additive (see Tables I and II on pages 14 and 15 of Appellants' Specification).

ISSUES PRESENTED ON APPEAL

(1) Whether the claims are anticipated under 35 USC 102(b) by EP 0692252; and

(2) Whether the disclosure meets the requirements of 35 USC 112, first paragraph, i.e. whether the claims are enabled by the Specification.

GROUPING OF CLAIMS

Claims 21-33 and 35-40 are pending in this Appeal. All of the claims are grouped together.

THE REFERENCES

The sole reference applied is EP 0692252. EP '252 teaches that inulin, oligofructose and their derivatives have properties of value as a functional ingredient in the prevention of carcinogensis or in treatment of cancer. EP '252 also mentions, at page 3, that the composition containing inulin may also include "conventional chemotherapeutic products." However, no mention is made in page 3 of a possible synergistic anti-cancer effect of such combination. In Example 7 on page 12, a combination of inulin/oligofructose and an anti-mitotic antibiotic is

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disclosed. However, no mention is made of a combination of inulin and an anti-metabolic anti-cancer drug as providing a synergistic anti-cancer effect.

ARGUMENT ON APPEAL

I. The rejection of the claims as being anticipated by EP' 252 is in error.

Before considering the art rejection in detail, it appears from Examiner's comments in the Final Action that the Examiner may be misreading the claims. More particularly, the Examiner states in the penultimate paragraph on page 2 of the Final Action:

> "Applicant's claims are drawn to the use of insulin (sic) and an antimetabolite in combination or separately for treatment of cancer in general...Furthermore, some of the claims are directed to the separate use of insulin (sic) and a metabolite (sic)". (Underlining added for emphasis).

Appellants submit that all of the claims are directed to a combination of inulin and an antimetabolite, more particularly an anti-metabolic anti-cancer drug. Independent claim 1 specifically requires, in part:

> "Pharmaceutical composition characterized by comprising a combination of an effective dose of inulin and of an anti-metabolic anti-cancer drug...".

All of the other claims are either directly or indirectly dependent on claim 21, or are linked to claim 21. Thus, all of the claims directed to a combination of inulin and an anti-metabolic anti-cancer drug for treatment of cancer, or a method for treatment of cancer using the claimed combination of inulin and an anti-metabolic anti-cancer drug.

Moreover, independent claim 21 specifies "wherein said inulin and said anti-metabolic anti-cancer drug in combination provide a synergistic anti-cancer therapeutic effect...". The term "synergistic" is defined in the On-line Medical Dictionary as "Acting together...". **(Exhibit B)**.

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Thus, the term "combination" is specifically recited twice in independent claim 21, and is also inferred by the term "synergistic" found in independent claim 21. The invention on appeal is all about the synergistic effect of the claimed combinations. Yet, the Examiner has chosen to thrice ignore in a five line claim the "combination" limitations. Needless to say, the Examiner cannot make out a case for anticipation by ignoring essential claim limitations.

All of the claims on Appeal have been rejected under 35 USC §102(b) as being anticipated by EP '252. Applicants submit that EP '252 neither anticipates nor, for that matter, renders obvious any of the claims on Appeal.

As pointed out by MPEP §2131:

> TO ANTICIPATE A CLAIM, THE REFERENCE MUST TEACH EVERY ELEMENT OF THE CLAIM
>
> 'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). > 'When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is [sic] known in the prior art. *Brown v. 3M*, 265 F.3d 1349, 1351, 60 USPQ2d 1375, 1376 (Fed. Cir. 2001) ... .' See also MPEP § 2131.02. < 'The identical invention must be shown in as complete detail as is contained in the ... claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

In rejecting the claims as anticipated by EP '252, the Examiner takes the position:

> "The prior art clearly teaches the combination of the claimed oligofructose in combination with an antimetabolite. The synergistic property of such combination is the inherent property of the composition". (Detailed Action, p. 2, ¶2).

In essence, the Examiner acknowledges the synergism of the claimed combination is not taught in the prior art, but the Examiner takes the position that such synergism is an "inherent

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property" of the disclosed composition. Actually, it is submitted that EP '252 fails to teach (1) the claimed combination, and (2) the claimed synergism.

At best EP '252 teaches the use of inulin and/or oligofructose for the manufacture of a medicament that is suitable for the prevention of mammary carcinogenesis and/or the treatment of breast cancer. EP '252 further discloses on page 3, lines 5-6, that in a particular embodiment the pharmaceutical composition may comprise "conventional chemotherapeutic products actively destroying malignant tumor cells." According to EP '252 these "conventional chemotherapeutic products are described on pages 249-253 of the "Répertoire Commenté des Médicaments," a publication of the Centre Belge d'lnformation Pharmacotherapeutique (1989)[1]. EP '252 further provides, on page 3, lines 8-20, an exhaustive generic list of classes of chemotherapeutic products considered as useful, together with examples of specific products for each of said classes as follows:

- alkylating compounds which possess alkyl groups highly reactive to specific biomolecules such as DNA (such as chlorambucil, cyclophosphamide, melphalan, carmustine, lomustine, busulfan, cisplastin, thiotepa, chlororimethin, lfosfamide, carboplastin, ... and their derivatives),
- antimetabolites which are used instead of the nucleic acids metabolites by the tumour cell (such as methotrexate, cytarabin, fluorouracil, mercaptopurin, thioguanin, azathioprin, hydroxy-carbamide, ...and their derivatives),
- antimitotic antibiotics (such as daunorubicin, bleomycin, mitomycin, ...and their derivatives),
- antitumoral alcaloids (such as vinblastin, vindesin, vincristin, ...and their derivatives),
- interferons (preferably interferon alpha),
- hormones and antihormones (such as fosfestrol, polyestrodiol, testolactone, tamoxifene, ...and their derivatives) and
- other specific therapeutic products (such as amsacrin, teniposide, procarbazin, etoposide, ...and their derivatives).

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[1] Of record and enclosed herewith as **Exhibit C** for the convenience of the Board.

Notably missing from this list of useful classes of chemotherapeutic products is any mention of an anti-metabolic anti-cancer drug!

Thus, the disclosure of EP '252 is merely a generic disclosure. No specific mention of a combination of inulin/oligofructose and an anti-metabolic anti-cancer product is disclosed, and no indication at all is given in EP '252 regarding a possible synergistic effect from the appropriate selection, method of selection, or basis of selection of inulin and an anti-metabolic anti-cancer drug.

Admittedly, Example 7 of EP '252 (page 10, lines 41-47) mentions that to determine potential synergistic therapeutic effects, a pharmaceutical composition comprising RAFTILINE® (trade name for chicory inulin of ORAFTI, Tienen (Belgium)) and a conventional chemotherapeutic product actively destroying malignant tumor cells, is prepared and a test is described wherein doxorubicine (an anti-cancer drug of the class of anti-mitotic antibiotics) was injected into mice-fed oligofructose/RAFTILINE® and which were previously inoculated with L1210 leukaemic tumor cells. However, EP '252 is completely silent about the outcome of the test or possible synergistic anti-cancer effects of a combination of inulin and doxorubicine, or for that matter inulin/oligofructose and conventional anti-cancer drugs.

Thus, there is no teaching contained within the four corners of EP '252 of a synergistic anti-cancer effect between inulin/oligofructose and a chemotherapeutic product. That is to say, a synergistic anti-cancer effect is neither disclosed nor taught in EP '252, and hence the teaching of EP '252 regarding compositions that may contain in addition to the inulin/oligofructose a chemotherapeutic product has to be seen merely as teaching compositions seeking the mere addition of the effects of both active ingredients. With respect to the combination of the subject claimed invention of inulin/oligofructose and an anti-

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metabolitic anti-cancer drug presenting synergistic anti-cancer effects, EP '252 therefore is completely silent and is a non-enabling disclosure.

Thus, contrary to the position taken by the Examiner, the prior art (EP '252) does not disclose a combination of inulin/oligofructose and "an anti-metabolic drug," but rather at best discloses a combination of inulin/oligofructose and an "anti-mitotic antibiotic," being the only substantiated combination of inulin/oligofructose and a chemotherapeutic product disclosed in EP '252. Based upon the disclosures of the "Répertoire Commenté des Médicaments" (1989), "anti-metabolic" drugs and "anti-mitotic antibiotics" belong to clearly different classes of chemotherapeutic products. Thus, the claims of the subject Application, which specifically read only on a combination of inulin/oligofructose and "an anti-metabolic drug," do not and cannot be said to read on of the EP '252 prior art.

Summarizing to this point, EP '252 neither explicitly discloses nor suggests within its four corners a composition according to the present claimed invention containing a combination of inulin and an anti-metabolic anti-cancer drug, or that such combination exhibits synergistic anti-cancer therapeutic effect. Therefore, the subject matter of independent claim 21 cannot be said to be anticipated by EP '252.

In contrast to the mechanical arts, the biological arts are considered by the courts to be "unpredictable." That is, a particular result with one system does not necessarily mean one will observe a comparable result with a different, though analogous, system. See, for example, *Genetich, Inc. v. Novo Nordisk*, 108 F.3d 1361, 42 USPQ 1001 (Fed. Cir. 1997). The present claimed invention concerns pharmaceutical compositions and their effect on living organisms. Living organisms are notoriously unpredictable, and the effect of pharmaceutical compositions on living organisms also is unpredictable. The claims of the present invention specifically are

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directed to the combination of inulin and an anti-metabolic anti-cancer drug. Amongst the large group of chemotherapeutic products, anti-metabolic anti-cancer drugs form a particular, well delimited class of compounds. The invention, as claimed, is neither disclosed nor suggested within the four corners of EP '252. The particular combination of inulin and an anti-metabolic anti-cancer drug as claimed in the subject application is endowed with special synergistic properties that are not taught by the prior art and could not be expected in view of the prior art, namely, that said particular claimed combination would present synergistic anti-cancer effect.

Moreover, the addition of inulin to the combination according to the present claimed invention clearly enhances the therapeutic anti-cancer effects of anti-metabolite anti-cancer drugs (see Specification, Examples (p. 12-13), Table 1 (p. 14) and Table 2 (p. 15)). Indeed, from Table 1 it is seen that the therapeutic anti-cancer effects of a combination of 5-fluorouracil and dietary FOS (i.e. inulin) are significantly higher than the sum of the effects of both components taken separately (see ISL (%): combination (40:6); 5 fluorouracil (18.75) and FOS (12.5)). A similar effect is shown in Table 2 for the combinations methotrexate and FOS, and methotrexate and inulin, compared to the sum of the effects of the components taken separately (see ISL (%): combination (29) and (20.5) respectively; methotrexate (2); FOS (5) and inulin (11)).

Since the anti-cancer effects of the combinations according to the invention are significantly higher than the sum of the anti-cancer effects of the components taken separately, the combination provides a synergistic effect. Thus, the properties of a composition containing a combination according to the present claimed invention are both novel and unexpected in

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view of the prior art, even in view of the generic disclosures on page 3, lines 5-20 and page 10, lines 41-47, of EP '252.

Moreover, as noted in the paragraph bridging pages 5-6 of Appellants' Specification, inulin is essentially non-digestible, and therefore generally considered as "soluble dietary fibers." Thus, it must be considered unobvious that combining inulin, an essentially non-digestible fiber supplement, with a specific class of anti-metabolic anti-cancer drugs would result in a synergistic effect or potentiation of the anti-cancer effect of an anti-metabolic anti-cancer drug. Thus, not only is Appellants' claimed invention novel, it is non-obvious.

Furthermore, on the basis of the prior art, including EP '252, and particularly in view of the uncertainty and unpredictability of the effect of pharmaceutical compositions on living organisms, one skilled in the art could not predict or expect that a particular combination of inulin/oligofructose and a particular class of anti-metabolic anti-cancer chemotherapeutic products would present a synergistic anti-cancer effect. This is furthermore evidenced by the experimental data presented in Table 1, p. 14 of Appellants' specification. These data clearly support the claimed criticality to the synergistic anti-cancer effect of the claimed combination of inulin and an anti-metabolic drug.

Thus, the rejection of the claims as being anticipated by EP '252 is in error and should be reversed.

II. The rejection of the claims under 35 USC 112, first paragraph is in error.

Turning to the rejection of the claims under 35 USC 112, first paragraph, the Examiner acknowledges that the data in the Specification demonstrates the use of the combination with at least one anti-metabolite and inulin; however, the Examiner takes the position that the claims are not commensurate in scope with the Specification:

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> "The presented data in the specification use the combination of only one antimetabolite and insulin (sic). Such data are not commensurate in scope with the claimed (sic) language...The state of the rat (sic) does not recognize that the treatment of all kinds of cancer is accomplished with one pharmaceutical composition".

Appellants submit that this rejection likewise is in error.

As pointed out by the Board of Appeals in its decision in Appeal No. 1996-3409, "It is well settled that the examiner bears the initial burden of providing reasons why a supporting disclosure does not enable a claim." In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). In the instant case, the Examiner's principal position is that undue experimentation would be required to practice the claimed invention because "the specification, while being enabling for the treatment of certain cancers, does not reasonably provide enablement for "the treatment of cancer" in general". The Examiner apparently also is concerned with the "considerable amount of invitro empirical testing [is] required with no prior expectation of success being present, before a candidate anti-cancer agent can be considered useful against any particular cancer type". (See pages 2 and 4 of the previous Action informally incorporated by reference in the Final Rejection).

While Applicants' claims admittedly are broad, they are not overly broad. All of Applicants' claims specify a particular material inulin, and a particular type of anti-cancer drug, namely, an anti-metabolic anti-cancer drug. Both of these ingredients are well known. Applicant is not claiming to have invented a new anti-metabolic anti-cancer drug candidate. Rather, Applicants' claims are all directed to the synergistic combination of a particular material, inulin, and a particular type of anti-cancer drug, an anti-metabolic anti-cancer drug. Since the anti-metabolic anti-cancer drugs already would have undergone invitro empirical testing, the only additional testing required would be to test a combination of inulin and a

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known anti-metabolic anti-cancer candidate drug, i.e., to determine if there is a synergistic effect from the combination. As stated in PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996):

> [T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

The Patent and Trademark Office Board of Appeals summarized this point in Ex parte Jackson, 217 USPQ 804, 807 (1982):

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentations should proceed to enable the determination of how to practice a desired embodiment of the invention.

Moreover, it is well settled that the specification need not disclose what is well known in the art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986).

Here, the Examiner has not presented any evidence that one skilled in the art would be unable to identify anti-metabolic anti-cancer drugs.

Moreover, though cancer is commonly known as a disease that can appear under the form of several kinds (types) of cancer, cancer is also known to be a disease that arises and proceeds according to a mechanism that is similar for the various kinds of cancer (see e.g. Specification, p.1, lines 15-31).

Accordingly, an anticancer drug belonging to one class of chemotherapeutic compounds (which by definition interferes with a certain step of the genesis or progression of the cancer [see Specification, p.2, lines 18-28]), generally presents anti-cancer effects against a wide range

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of kinds of cancer (since all these kinds of cancer arise and proceed through a same or very similar mechanism). This consequently also applies to the class of antimetabolites.

Support for the above is provided by Medline Plus® for several typical antimetabolites that are mentioned in the listing of the chemotherapeutic products "Répertoire commenté des médicaments, Centre Belge d'information pharmacothérapeutique, 1987, p.341-345 ", for example fluorouracil, methotrexate, cytarabine, mercaptopurine, thioguanine and hydroxycarbamide (see the excerpts from Medline Plus® Drug information and the summary thereof, given in Table 1, of record and enclosed herewith for the convenience of the Board as **Exhibit D**).

Furthermore, Appellants submit that when considering the treatment of a particular kind of cancer using a pharmaceutical composition defined in any of the rejected claims, one skilled in the art would not be confronted with an undue burden to define the particulars of the composition and/or the method of treatment to be used for a given antimetabolite and/or a given kind of cancer. Indeed, the required information is readily available from the prior art for each antimetabolite and each kind of cancer, while the person skilled in the art easily can determine whether the anti-cancer effect of said antimetabolite is enhanced by its combination with inulin by simple experimentation.

It must be remembered that "cancer" is essentially a condition resulting from cells which, due to alterations of their DNA, start proliferating in an uncontrolled manner, with invasion of organs and bodily structures, thereby jeopardizing good functioning of said organs and structures, which may lead to disenablement and eventually to the death of the affected being. So, cancer is known to be a disease that arises and proceeds accordingly to a mechanism that is the same for the various kinds (types) of cancer. (See e.g. Specification, page 1, lines 15-

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31). Accordingly, the term "cancer" refers in fact to a single disease which may appear in various kinds.

Furthermore, as evidenced in the Specification (see Table 1 and Table 2), the anti-cancer effects presented by anti-metabolite anti-cancer drugs are enhanced in a synergistic manner by the interaction of the anti-metabolite anti-cancer drug with inulin in combinations according to the claimed invention.

Quite apart from the foregoing, it is noted Appellants have proven that the synergistic anti-cancer effect of the combination of inulin/oligofructose and an anti-metabolic anti-cancer drug is not limited to a single anti-metabolic anti-cancer drug as stated by the Examiner. Rather, Appellants have demonstrated a synergistic effect of the combination with two different anti-metabolic anti-cancer drugs, namely fluoronraul and methotrexate (See Tables I and II). Appellants submit therefore that, having supported the claimed pharmaceutical composition by two examples, their claims to a combination of inulin/oligofructose and a drug from the specific and defined class of anti-metabolic anti-cancer drugs satisfy the requirements of 35 USC §112, first paragraph, and the rejection of the claims under 35 USC §112, first paragraph, is in error.

CONCLUSION

In view of the above comments, the present invention, which claims a combination of inulin and an anti-metabolic anti-cancer drug (a specific class of chemotherapeutic products that is clearly different from the class of anti-mitotic antibiotics), has thus to be considered both novel and non-obvious in view of EP '252, and enabled.

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Accordingly, it is respectfully requested that the Examiner's Rejection of the subject Application be reversed in all respects.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: MAIL STOP APPEAL BRIEF-PATENTS, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on August 11, 2005, at Tucson, Arizona.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE APPLN. OF: TAPER et al.

SERIAL NO.: 09/700,573

FILED: November 16, 2000

FOR: SYNERGISTIC COMPOSITION FOR USE IN THE TREATMENT...

GROUP: 1614

EXAMINER: ZOHREH A. FAY DOCKET: TIENSE RAFF.28

MAIL STOP APPEAL BRIEF - PATENTS
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APPENDIX A

APPELLANTS' BRIEF ON APPEAL

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APPENDIX A

CLAIMS ON APPEAL

21. Pharmaceutical composition characterized by comprising a combination of an effective dose of inulin and of an anti-metabolic anti-cancer drug, wherein said inulin and said anti-metabolic anti-cancer drug in combination provide a synergistic anti-cancer therapeutic effect to a human or non-ruminating animal undergoing treatment for cancer.

22. Pharmaceutical composition according to claim 21, wherein the inulin is inulin with a DP up to about 100, or oligofructose or a mixture thereof.

23. Pharmaceutical composition according to claim 21, wherein the inulin is chicory inulin with a ($\overline{DP}$) ranging from about 10 to about 30, or oligofructose with a (DP) ranging from 2 to 7 and containing about 5 wt% in total of glucose, fructose and sucrose.

24. Pharmaceutical composition according to claim 21, wherein the anti-cancer drug is selected from the group consisting of methotrexate, cytarabin, fluorouracil, mercaptopurin, thioguanin, azathioprin and hydroxycarbamide.

25. Pharmaceutical composition according to claim 24 wherein the anti-cancer drug is 5-fluorouracil or methotrexate.

26. Pharmaceutical composition according to claim 21, which additionally to the said anti-metabolic anti-cancer drug contains one or more anti-cancer drugs belonging to the class of anti-metabolic anti-cancer drugs and/or to another class of anti-cancer drugs.

27. Pharmaceutical composition according to claim 21, in which the inulin and the anti-metabolic anti-cancer drug which constitute the combination are present in the same galenic formulation.

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28. Pharmaceutical composition according to claim 21, in which the inulin and the anti-metabolic anti-cancer drug which constitute the combination are present in separate galenic formulations which in combination together form the pharmaceutical composition.

29. Pharmaceutical composition according to claim 21, which is suitable for oral, parenteral or rectal administration, or for tube feeding.

30. Pharmaceutical composition according to claim 28 in which the inulin is present in a functional food or feed.

31. Pharmaceutical composition according to claim 28 in which the anti-cancer drug is present in a formulation which is suitable for oral or parenteral administration.

32. Pharmaceutical composition according to claim 21 for use as a medicament for the treatment of cancer in human.

33. Pharmaceutical composition according to claim 21 for use as a medicament for the treatment of cancer in non-ruminating mammals.

35. Method for the treatment of cancer in a human or in a non-ruminating mammal comprising administering to said being in need of such treatment an effective amount of a pharmaceutical composition as defined in claim 21.

36. Method according to claim 35 wherein the inulin and the anti-metabolic anti-cancer drug of the combination forming the pharmaceutical composition are present in the same galenic formulation constituting the pharmaceutical composition.

37. Method according to claim 35 wherein the inulin and the anti-metabolic anti-cancer drug of the combination forming the pharmaceutical composition are present in separate galenic formulations constituting together the pharmaceutical composition.

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38. Method according to claim 37 wherein the separate galenic formulations are administered simultaneously or non-simultaneously.

39. Method according to claim 37 wherein the separate galenic formulations are administered via different methods of administration and the inulin is administered by a method selected from the group consisting of oral, parenteral or rectal administration and administration via tube feeding.

40. Method according to claim 39 wherein the separate galenic formulation containing the inulin is a functional food or feed.

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APPENDIX B

APPELLANTS' BRIEF ON APPEAL

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synergistic

<pharmacology, physiology> Acting together, enhancing the effect of another force or agent.

(19 Jan 1998)

Previous: synergetic, synergia, synergic, synergic control, synergism, synergist
Next: synergistic effect, synergistic muscles, synergy, synesthesia

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APPENDIX C

APPELLANTS' BRIEF ON APPEAL

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REPERTOIRE COMMENTE DES MEDICAMENTS

1987

CENTRE BELGE
D'INFORMATION PHARMACOTHERAPEUTIQUE

ANTITUMORAUX

Ce chapitre reprend successivement:
- les agents alkylants
- les antimétabolites
- les antibiotiques antimitotiques
- les alcaloïdes antitumoraux
- divers antitumoraux.

Les hormones ou antihormones utilisées notamment dans les cancers du sein, des organes génitaux féminins et de la prostate sont reprises avec les médicaments du système hormonal.

Les médicaments antitumoraux sont responsables d'effets toxiques dont la gravité peut détériorer la qualité de la survie. Ceux-ci doivent être décelés aussi précocement que possible. La dépression de la moelle osseuse favorise des infections graves et provoque des hémorragies par thrombopénie; des contrôles hématologiques réguliers sont donc nécessaires. La destruction des cellules néoplasiques peut entraîner une hyperuricémie que l'allopurinol permet éventuellement de corriger. L'action irritante habituelle de ces substances sur les muqueuses digestives est souvent à l'origine de nausées, de vomissements et de diarrhée même lors d'administration parentérale. L'alopécie est d'apparition fréquente. La chimiothérapie est dangereuse pour l'embryon; au cours du traitement une méthode de contraception efficace sera préconisée chez les femmes en âge de procréer. Une atteinte de la fonction ovarienne ou de la spermatogenèse, avec risque de stérilité chez l'homme, est souvent observée spécialement avec les agents alkylants.

Plusieurs de ces médicaments sont très irritants localement et peuvent provoquer des nécroses lors d'injection paraveineuse accidentelle.

Les effets indésirables particuliers à chaque groupe ou à chacun de ces médicaments sont mentionnés aux rubriques respectives.

Les médicaments antitumoraux sont délicats à manier et leur emploi requiert de l'expérience. Les options thérapeutiques relèvent du spécialiste. Les indications, la posologie et le mode d'emploi de ces médicaments (solvants, mode de préparation précis des solutions) ne sont donc pas repris ici.

Pour les spécialités à usage hospitalier (U.H.) seul le plus petit conditionnement a été repris.

1. Agents alkylants

Ces substances possèdent des groupements alkyles hautement réactifs qui se lient à certaines biomolécules et en particulier à l'ADN. Elles inhibent ainsi la multiplication cellulaire, principalement dans les tissus à activité mitotique élevée.

Selon leur structure chimique, on les divise en dérivés de l'ypérite (moutardes à l'azote): chlorambucil, chlorméthine, cyclophosphamide et melphalan, en nitroso-urées: carmustine et

lomustine, et autres dérivés appartenant à des classes chimiques variées: busulfan, cisplatine et thiotépa.

Ces médicaments peuvent provoquer une atteinte de la fonction ovarienne et de la spermatogenèse ainsi qu'une fibrose pulmonaire; ils sont tératogènes et cancérogènes.

ALKERAN (Wellcome)

melphalan
compr. 25 × 2 mg R/ 347 F (a)
flacon i.v. - in situ
1 × 100 mg poudre
+ 9 ml solv. R/ 952 F (a)

CECENU (Rhône-Poulenc)

lomustine
caps. 50 × 40 mg U.H.

CYCLOBLASTINE (Farmitalia Carlo Erba)

cyclophosphamide
drag. 50 × 50 mg R/ 247 F (a)
flacon i.v.
10 × 100 mg poudre R/ 385 F (a)
10 × 200 mg poudre R/ 529 F (a)
10 × 500 mg poudre R/ 1041 F (a)
1 × 1 g poudre R/ 267 F (a)
(cystite hémorragique; aussi utilisé comme immunosuppresseur,
autre marque déposée: Endoxan)

ENDOXAN (Asta Werke/Cilag)

cyclophosphamide
drag. 50 × 50 mg R/ 247 F (a)
flacon i.v. (i.m. éventuellement)
10 × 100 mg poudre R/ 385 F (a)
10 × 200 mg poudre R/ 529 F (a)
flacon i.v. 5 × 500 mg poudre R/ 575 F (a)
(cystite hémorragique, aussi utilisé comme immunosuppresseur
autre marque déposée: Cycloblastine)

ESTRACYT (Leo/Bios-Coutelier)

estramustine phosphate
caps. 40 × 140 mg R/ 3490 F (a)
100 × 140 mg R/ 7300 F (a)
flacon i.v. 10 × 300 mg + 8 ml solv.
R/ 4227 F (a)
(gynécomastie, rétention hydrique)

LEDERTEPA (Lederle/Cyanamid)

thiotépa
flacon i.m. - i.v. - in situ
1 × 15 mg poudre R/ 157 F (a)
(autre marque déposée: Oncotiotepa)

LEUKERAN (Wellcome)

chlorambucil
drag. 25 × 5 mg R/ 413 F (a)
(aménorrhée, azoospermie)

MUSTINE CHLORH. B.P. (Boots)

chlorméthine chlorhydrate
flacon i.v. 10 mg poudre U.H.
(symptômes cholinergiques: diarrhée, myosis, vomissements, nécrose tissulaire en cas d'extravasation)

MYLERAN (Wellcome)

busulfan
compr. 100 × 2 mg R/ 638 F (a)
(gynécomastie, éruption cutanée, hyperpigmentation)

NITRUMON (Sintesa)

carmustine
flacon i.v. 1 × 100 mg poudre R/ 953 F (a)
(toxicité hépatique et rénale, vertiges, perte d'équilibre, ataxie)

ONCOTIOTEPA (Sintesa)

thiotépa
amp. i.m. - i.v. - intra-artériel - in situ
5 × 10 mg + 5 × 4 ml solv. R/ 176 F (a)
(autre marque déposée: Ledertepa)

PLATINOL (Bristol)

cisplatine
flacon i.v. 10 mg/ 20 ml U.H.
25 mg/ 50 ml U.H.
50 mg/100 ml U.H.
flacon i.v. 50 mg poudre U.H.
(toxicité rénale, ototoxicité, neurotoxicité, réactions de type anaphylactique
autre marque déposée: Platistine)

PLATISTINE (Farmitalia Carlo Erba)

cisplatine
flacon i.v. 10 mg poudre U.H.
25 mg poudre U.H.
50 mg poudre U.H.
(toxicité rénale, ototoxicité, neurotoxicité, réactions de type anaphylactique
autre marque déposée: Platinol)

[redacted]

2. Antimétabolites

Les antimétabolites entrent en compétition avec des métabolites normaux de la chaîne de synthèse cellulaire des acides nucléiques. Ils sont souvent utilisés en même temps que d'autres cytostatiques. Parmi les antimétabolites actuellement disponibles, on trouve un antagoniste de l'acide folique (méthotrexate), des antagonistes des bases pyrimidiniques ou puriques (cytarabine, fluorouracile, mercaptopurine, tioguanine), l'azathioprine (décrite au chapitre Immunosuppresseurs) et enfin l'hydroxycarbamide. Le méthotrexate est de plus utilisé dans des cas graves de psoriasis mais il s'agit là d'une thérapeutique d'exception en raison des effets indésirables de ce médicament. Le fluorouracile est également utilisé dans des kératoses et tumeurs cutanées sous forme de préparations locales (v. chapitre Préparations à usage dermatologique).

Les antimétabolites présentent les effets indésirables communs à tous les cytostatiques. En outre, ils peuvent causer une mégaloblastose, des lésions du foie et du tube digestif (stomatites, ulcérations buccales et parfois gastro-intestinales). Le méthotrexate peut aussi être responsable de fibrose pulmonaire, d'ostéoporose, de toxicité rénale et d'éruptions cutanées.

ALEXAN (Mack/de Bournonville)

cytarabine
amp. i.m. - i.v. - intra-rach - s.c.
10 × 40 mg/ 2 ml R/ 1056 F (a)
30 × 40 mg/ 2 ml R/ 2888 F (a)
10 × 100 mg/ 5 ml R/ 1662 F (a)
1 × 500 mg/25 ml R/ 1003 F (a)
(convulsions
autre marque déposée: Cytosar)

CYTOSAR (Upjohn)

cytarabine
flacon i.v.
1 × 100 mg poudre + 5 ml solv. R/ 275 F (a)
1 × 500 mg poudre + 10 ml solv. R/ 1003 F (a)
(convulsions
autre marque déposée: Alexan)

EMTHEXATE (Conforma)

méthotrexate
flacon i.v. 1 × 5 mg poudre R/ 139 F (a)
1 × 50 mg poudre U.H.
1 × 500 mg poudre U.H.
1 × 1 g poudre U.H.
(remarque: voir Ledertrexate SP
autre marque déposée: Ledertrexate)

FLUORO-URACIL (Roche)

fluorouracile
amp. i.v. 5 × 250 mg/10 ml R/ 623 F (a)
(neurotoxicité, ataxie cérébelleuse, hyperpigmentation, photosensibilisation)

HYDREA (Squibb)

hydroxycarbamide
caps. 20 × 500 mg R/ 330 F (a)

LANVIS (Wellcome)

tioguanine
compr. séc. 25 × 40 mg R/ 1154 F (a)

LEDERTREXATE (Lederle/Cyanamid)

méthotrexate
compr. 100 × 2,5 mg R/ 665 F (a)
(remarque: voir Ledertrexate SP
autre marque déposée: Emthexate)

LEDERTREXATE SODIUM (Lederle/Cyanamid)

méthotrexate
flacon i.m. - i.v. - intra-artériel
12 × 5 mg poudre R/ 1348 F (a)
1 × 50 mg poudre U.H.
1 × 500 mg poudre U.H.
(remarque: voir Ledertrexate SP
autre marque déposée: Emthexate)

LEDERTREXATE SP (Lederle/Cyanamid)

méthotrexate
amp. intrathécale
1 × 5 mg/2 ml R/ 177 F (a)
1 × 50 mg/2 ml U.H.
(SP: sans agent conservateur;
par voie intrathécale: méningisme et convulsions, rarement encéphalite nécrosante;
l'acide folinique (*LEDERVORIN Ca*^{R} - chapitre Vitamines) est souvent associé au traitement par méthotrexate comme antidote)

PURI-NETHOL (Wellcome)

mercaptopurine
compr. 25 × 50 mg R/ 545 F (a)
(doses à réduire en cas d'administration concomitante d'allopurinol)

3. Antibiotiques antimitotiques

Plusieurs antibiotiques produits par différentes souches de streptomyces et trop toxiques pour être utilisés comme antibactériens sont doués de propriétés antitumorales.

La mithramycine est également utilisée dans des hypercalcémies d'origine maligne ou pagétique.

Toutes ces substances présentent les effets indésirables des autres cytostatiques sauf la bléomycine qui n'a pas de toxicité hématologique; il existe aussi une cardiotoxicité.

ADRIBLASTINA (Farmitalia Carlo Erba)

doxorubicine
flacon i.v. 1 × 10 mg poudre
+ 5 ml solv. R/ 1034 F (a)
5 × 10 mg poudre
+ 5 ml solv. R/ 3695 F (a)
1 × 50 mg poudre + solv. U.H.
(cardiotoxicité, stomatite, nécrose tissulaire en cas d'extravasation)

BLEOMYCINE (Bellon/Wellcome)

bléomycine
flacon i.m. - i.v. - intra-artériel - in situ
1 × 15 mg poudre R/ 1234 F (a)
(fibrose pulmonaire, éruptions cutanées, stomatite, hyperpigmentation, sclérose digitale, syndrome de Raynaud)

CERUBIDINE (Rhône-Poulenc)

daunorubicine
flacon i.v. 1 × 20 mg poudre
+ 4 ml solv. R/ 549 F (a)
(cardiotoxicité, stomatite, nécrose tissulaire en cas d'extravasation)

FARMORUBICINE (Farmitalia Carlo Erba)

épirubicine chlorhydrate
flacon i.v. 10 mg poudre R/ 1137 F (a)
50 mg poudre R/ 4317 F (a)
(cardiotoxicité, stomatite, nécrose tissulaire en cas d'extravasation)

LYOVAC COSMEGEN (M.S.D.)

dactinomycine
flacon i.v.
1 × 0,5 mg poudre R/ 145 F (a)
(réactions locales et phlébites, ulcérations digestives, érythème, hyperpigmentation, acné)

MITOMYCINE (Christiaens)

mitomycine c
flacon i.v. - intra-artériel
10 × 2 mg poudre R/ 2647 F (a)
3 × 10 mg poeder R/ 3625 F (a)
(réactions locales, stomatite, nécrose tissulaire en cas d'extravasation)

NOVANTHRONE (Lederle/Cyanamid)

mitoxantrone
flacon i.v. 20 mg/10 ml R/ 8988 F (a)
25 mg/12,5 ml R/ 11150 F (a)

4. Alcaloïdes antitumoraux

Ces substances bloquent la mitose en métaphase. Trois alcaloïdes de la pervenche sont utilisés en clinique: la vinblastine, la vincristine et la vindésine. En plus des effets indésirables habituels des cytostatiques (mise à part la dépression médullaire qui est plus rare) ils peuvent être responsables d'asthénie, de troubles visuels, de constipation et parfois d'iléus paralytique ainsi que de polynévrite. Cette toxicité neurologique s'observe surtout avec la vincristine. Une sécrétion inappropriée d'hormone antidiurétique a également été signalée.

ELDISINE (Eli Lilly)

vindésine sulfate
flacon i.v. 1 × 1 mg poudre R/ 1512 F (a)
1 × 5 mg poudre R/ 4558 F (a)

ONCOVIN (Eli Lilly)

vincristine sulfate
flacon i.v. 1 × 1 mg poudre
+ 10 ml solv. R/ 837 F (a)
1 × 2 mg poudre
+ 10 ml solv. R/ 1248 F (a)
1 × 5 mg poudre
+ 10 ml solv. R/ 2923 F (a)

VELBE (Eli Lilly)

vinblastine sulfate
flacon i.v. 1 × 10 mg poudre R/ 896 F (a)
(stomatite)

5. Interféron

L'interféron α_2 b peut être utilisé en cas d'affections hématologiques malignes et de maladies s'accompagnant de déficience immunitaire. Une dépression du système nerveux central, de la confusion, des éruptions cutanées, une stomatite et des troubles de la coagulation ont été décrits.

INTRON A (Schering Corp. Essex)

alfa-2 b interféron
flacon s.c. - inf. 3×10^6 UI R/ 1753 F
5×10^6 UI R/ 2590 F
10×10^6 UI R/ 4682 F
30×10^6 UI R/ 13 053 F

6. Antitumoraux divers

L'étoposide et le téniposide sont des dérivés semi-synthétiques de la podophyllotoxine. Leurs effets indésirables sont ceux des cytostatiques en général.

L'aminoglutéthimide est utilisé dans les tumeurs du sein hormono-dépendantes et dans le syndrome de Cushing.

L'amsacrine est un dérivé synthétique de l'acridine. Elle est utilisée dans le traitement des leucémies aiguës non lymphoblastiques qui n'ont pas répondu favorablement à d'autres traitements.

AMSIDINE (Parke-Davis)

amsacrine
flacon perf. 5 × 75 mg/1,5 ml
+ 13,5 ml solv. U.H.

DTIC-DOME (Miles/Frère)

dacarbazine
flacon i.v.
12 × 100 mg poudre R/ 2671 F (a)
(syndrome pseudogrippal, atteinte hépatique, paresthésies, éruptions cutanées, douleur au site d'injection)

NATULAN (Roche)

procarbazine
caps. 50 × 50 mg R/ 224 F (a)
(dépression du système nerveux central, neuropathie périphérique, effet inhibiteur des monoamine oxydases, effet disulfiram, stomatite, dermatite)

ORIMETEN (Ciba-Geigy)

aminoglutéthimide
compr. séc. 100 × 250 mg R/ 2258 F (b)

VEPESID (Bristol)

étoposide
caps. 10 × 100 mg R/ 4221 F (a)
amp. perf. 10 × 100 mg/5 ml R/ 5118 F (a)

VUMON (Bristol)

téniposide
amp. perf. 10 × 50 mg/5 ml R/ 2088 F (a)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE APPLN. OF: TAPER et al.

SERIAL NO.: 09/700,573

FILED: November 16, 2000

FOR: SYNERGISTIC COMPOSITION FOR USE IN THE TREATMENT...

GROUP: 1614

EXAMINER: ZOHREH A. FAY DOCKET: TIENSE RAFF.28

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPENDIX D

APPELLANTS' BRIEF ON APPEAL

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Drug Information: Fluorouracil (Systemic)

URL of this page: http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202245.html

Brand Names

In the U.S.—

- Adrucil

In Canada—

- Adrucil

Another commonly used name is 5-FU.

Category

- **Antineoplastic**

Description

Fluorouracil (flure-oh-YOOR-a-sill) belongs to the group of medicines known as antimetabolites. It is used to treat cancer of the colon, rectum, breast, stomach, and pancreas. It may also be used to treat other kinds of cancer, as determined by your doctor.

Fluorouracil interferes with the growth of cancer cells, which are eventually destroyed. Since the growth of normal body cells may also be affected by fluorouracil, other effects will also occur. Some of these may be serious and must be reported to your doctor. Other effects, like hair loss, may not be serious but may cause concern. Some effects may not occur for months or years after the medicine is used.

Before you begin treatment with fluorouracil, you and your doctor should talk about the good this medicine will do as well as the risks of using it.

Fluorouracil is to be administered only by or under the immediate supervision of your doctor. It is available in the following dosage form:

Parenteral
- Injection (U.S. and Canada)

Before Using This Medicine

In deciding to use a medicine, the risks of taking the medicine must be weighed against the good it will do. This

Check with your doctor or nurse immediately if any of the following side effects occur:

- *More common*
  - Diarrhea; heartburn; sores in mouth and on lips

- *Less common*
  - Black, tarry stools; cough or hoarseness, accompanied by fever or chills; fever or chills; lower back or side pain, accompanied by fever or chills; nausea and vomiting (severe); painful or difficult urination, accompanied by fever or chills; stomach cramps

- *Rare*
  - Blood in urine or stools; pinpoint red spots on skin; unusual bleeding or bruising

Check with your health care professional as soon as possible if any of the following side effects occur:

- *Rare*
  - Chest pain; cough; shortness of breath; tingling of hands and feet, followed by pain, redness, and swelling; trouble with balance

Other side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects. Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:

- *More common*
  - Loss of appetite; nausea and vomiting ; skin rash and itching; weakness

- *Less common*
  - Dry or cracked skin

This medicine often causes a temporary loss of hair. After treatment with fluorouracil has ended, normal hair growth should return.

After you stop receiving fluorouracil, it may still produce some side effects that need attention. During this period of time, *check with your doctor or nurse immediately* if you notice any of the following:

- Black, tarry stools; blood in urine or stools; cough or hoarseness, accompanied by fever or chills; fever or chills; lower back or side pain, accompanied by fever or chills; painful or difficult urination, accompanied by fever or chills; pinpoint red spots on skin; unusual bleeding or bruising

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your health care professional.

Additional Information

Once a medicine has been approved for marketing for a certain use, experience may show that it is also useful for other medical problems. Although these uses are not included in product labeling, fluorouracil is used in certain patients with the following medical conditions:

- Cancer of the outside layer of the adrenal gland
- Cancer of the anus
- Cancer of the bladder
- Cancer of the cervix
- Cancer of the endometrium
- Cancer of the ovaries

- Cancer of the esophagus
- Cancer of the head and neck
- Cancer of the penis
- Cancer of the liver
- Cancer of the prostate
- Cancer of the skin
- Cancer of the vulva
- Carcinoid tumors
- Hepatoblastoma (a certain type of liver cancer that occurs in children)
- Glaucoma, during and after certain surgery (trabeculectomy)

Other than the above information, there is no additional information relating to proper use, precautions, or side effects for these uses.

Revised: 05/04/2001

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Drug Information: Methotrexate For Cancer (Systemic)

URL of this page: http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202355.html

Brand Names

In the U.S.—

In Canada—

Another commonly used name is amethopterin.

Category

- **Antineoplastic**

Description

Methotrexate (meth-o-TREX-ate) belongs to the group of medicines known as antimetabolites. It is used to treat cancer of the breast, head and neck, lung, blood, bone, and lymph, and tumors in the uterus. It may also be used to treat other kinds of cancer, as determined by your doctor.

Methotrexate blocks an enzyme needed by the cell to live. This interferes with the growth of cancer cells, which are eventually destroyed. Since the growth of normal body cells may also be affected by methotrexate, other effects will also occur. Some of these may be serious and must be reported to your doctor. Other effects, like hair loss, may not be serious but may cause concern. Some effects may not occur for months or years after the medicine is used.

Before you begin treatment with methotrexate, you and your doctor should talk about the good this medicine will do as well as the risks of using it.

Methotrexate is available only with your doctor's prescription, in the following dosage forms:

Oral
- Tablets (U.S. and Canada)

Parenteral
- Injection (U.S. and Canada)

Before Using This Medicine

In deciding to use a medicine, the risks of taking the medicine must be weighed against the good it will do. This

- Back pain; cough or hoarseness accompanied by fever or chills; dark urine; dizziness; drowsiness; fever or chills; headache; lower back or side pain accompanied by fever or chills; painful or difficult urination accompanied by fever or chills; unusual tiredness or weakness; yellow eyes or skin

Other side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects. Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:

- *More common*
  - Loss of appetite; nausea or vomiting

- *Less common*
  - Acne; boils; pale skin; skin rash or itching

This medicine may cause a temporary loss of hair in some people. After treatment with methotrexate has ended, normal hair growth should return.

After you stop using methotrexate, it may still produce some side effects that need attention. During this period of time, check with your doctor as soon as possible if you notice any of the following side effects:

- Back pain; blurred vision; confusion; convulsions (seizures); dizziness; drowsiness; fever; headache; unusual tiredness or weakness

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

Additional Information

Once a medicine has been approved for marketing for a certain use, experience may show that it is also useful for other medical problems. Although these uses are not included in product labeling, methotrexate is used in certain patients with the following medical conditions:

- Acute nonlymphocytic leukemia (a type of cancer of the blood and lymph system)
- Cancer in the membranes that cover and protect the brain and spinal cord (the meninges)
- Cancer of the bladder
- Cancer of the brain (lymphoma)
- Cancer of the cervix
- Cancer of colon and rectum
- Cancer of the esophagus
- Cancer of the ovaries
- Cancer of the pancreas
- Cancer of the penis
- Cancers of the soft tissues of the body, including the muscles, connective tissues (tendons), vessels that carry blood or lymph, or fat
- Cancer of the stomach
- Hodgkin's lymphoma (a cancer of the lymph system, a part of the body's immune system)

Other than the above information, there is no additional information relating to proper use, precautions, or side effects for these uses.

Revised: 08/01/2000

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Drug Information: Cytarabine

URL of this page: http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682222.html

(sye tare' a been)

Brand name(s): Cytosar-U
Other name(s): Ara-C; Cytosine arabinoside

IMPORTANT WARNING:

Cytarabine can cause a decrease in the number of blood cells in your bone marrow. Your doctor will order tests before, during, and after your treatment to see if your blood cells are affected by this drug.

About your treatment

Your doctor has ordered the drug cytarabine to help treat your illness. The drug can be given by injection into a vein or under the skin of your forearm. In special situations, it may be injected into the spinal cord.

This medication is used to treat:

- certain types of leukemias

This medication is sometimes prescribed for other uses; ask your doctor or pharmacist for more information.

Cytarabine belongs to a group of drugs known as antimetabolites. It resembles a normal cell nutrient needed by cancer cells to grow. The cancer cells take up cytarabine, which then interferes with their growth.

Other uses for this medicine

Cytarabine also is used to treat non-Hodgkin's lymphoma. Talk to your doctor about the possible risks of using this drug for your condition.

Precautions

Before taking cytarabine,

- tell your doctor and pharmacist if you are allergic to cytarabine or any other drugs.
- tell your doctor and pharmacist what prescription and nonprescription medications you are taking, especially aminoglycoside antibiotics such as amikacin, gentamicin, netilmicin, and tobramycin; aspirin; digoxin (Lanoxin); flucytosine; and vitamins.
- tell your doctor if you have or have ever had kidney disease, liver disease, or gout.
- you should know that cytarabine may interfere with the normal menstrual cycle (period) in women and may stop sperm production in men. However, you should not assume that you cannot get pregnant or that you cannot get someone else pregnant. Women who are pregnant or breast-feeding should tell their doctors before they begin taking this drug. You should not plan to have children while receiving chemotherapy or for a while after treatments. (Talk to your doctor for further details.) Use a reliable

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Drug Information: Cytarabine (Systemic)

URL of this page: http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202177.html

Brand Names

In the U.S.—

- Cytosar-U

In Canada—

- Cytosar

Other commonly used names are ara-C; cytosine arabinoside.

Category

- **Antineoplastic**

Description

Cytarabine (sye-TARE-a-been) belongs to the group of medicines called antimetabolites. It is used to treat some kinds of cancers of the blood. It may also be used to treat other kinds of cancer, as determined by your doctor.

Cytarabine interferes with the growth of cancer cells, which are eventually destroyed. Since the growth of normal body cells may also be affected by cytarabine, other effects will also occur. Some of these may be serious and must be reported to your doctor. Other effects, like hair loss, may not be serious but may cause concern. Some effects may not occur for months or years after the medicine is used.

Before you begin treatment with cytarabine, you and your doctor should talk about the good this medicine will do as well as the risks of using it.

Cytarabine is to be administered only by or under the immediate supervision of your doctor. It is available in the following dosage form:

Parenteral
- Injection (U.S. and Canada)

Before Using This Medicine

In deciding to use a medicine, the risks of taking the medicine must be weighed against the good it will do. This

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

Additional Information

Once a medicine has been approved for marketing for a certain use, experience may show that it is also useful for other medical problems. Although these uses are not included in product labeling, cytarabine is used in certain patients with the following medical conditions:

- Cancer of the lymph system
- Cancer of the brain and spinal cord

Other than the above information, there is no additional information relating to proper use, precautions, or side effects for these uses.

Revised: 07/02/1998

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Drug Information: Mercaptopurine

URL of this page: http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682653.html

(mer kap toe pyoor' een)

Brand name(s): Purinethol
Other name(s): 6-MP

About your treatment

Your doctor has ordered the drug mercaptopurine to help treat your illness. The drug is taken by mouth in tablet form.

This medication is used to treat:

- leukemia

This medication is sometimes prescribed for other uses; ask your doctor or pharmacist for more information.

Mercaptopurine belongs to a group of drugs known as antimetabolites. It resembles a normal cell nutrient needed by cancer cells to grow. The cancer cells take up mercaptopurine which then interferes with their growth.

Other uses for this medicine

Mercaptopurine also is used to treat many types of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, acute idiopathic polyneuritis, acute idiopathic nephrotic syndrome, psoriatic arthritis, erythroid aplasia, or myelofibrosis; idiopathic hemolytic anemia; macroglobulinemia; idiopathic thrombocytopenia purpura; idiopathic pulmonary hemosiderosis; multiple sclerosis; myasthenia gravis; uveitis; and ulcerative colitis. Talk to your doctor about the possible risks of using this drug for your condition.

Precautions

Before taking mercaptopurine,

- tell your doctor and pharmacist if you are allergic to mercaptopurine or any other drugs.
- tell your doctor and pharmacist what prescription and nonprescription medications you are taking, especially allopurinol (Zyloprim), anticoagulants ('blood thinners') such as warfarin (Coumadin), aspirin, and vitamins.
- you should know that mercaptopurine may interfere with the normal menstrual cycle (period) in women and may stop sperm production in men. However, you should not assume that you cannot get pregnant or that you cannot get someone else pregnant. Women who are pregnant or breast-feeding should tell their doctors before they begin taking this drug. You should not plan to have children while receiving chemotherapy or for a while after treatments. (Talk to your doctor for further details.) Use a reliable method of birth control to prevent pregnancy. Mercaptopurine may harm the fetus.
- do not have any vaccinations (e.g., measles or flu shots) without talking to your doctor.

Side effects

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Drug Information: Thioguanine

URL of this page: http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682099.html

(thye oh gwah' neen)

Brand name(s): Tabloid
Other name(s): 6-TG, TG

About your treatment

Your doctor has ordered the drug thioguanine to help treat your illness. The drug can be taken by mouth in tablet form.

This medication is used to treat:

- leukemia

This medication is sometimes prescribed for other uses; ask your doctor or pharmacist for more information.

Thioguanine belongs to a class of medications known as antimetabolites. It resembles a normal cell nutrient needed by cancer cells to grow. The cancer cells take up thioguanine, which then interferes with their growth.

Precautions

Before taking thioguanine,

- tell your doctor and pharmacist if you are allergic to thioguanine or any other medications.
- tell your doctor and pharmacist what prescription and nonprescription medications you are taking, especially aspirin, busulfan (Myleran), mesalamine (5-ASA, Asacol, Pentasa, Rowasa), olsalazine (Dipentum), sulfasalazine (Azulfidine), and vitamins.
- tell your doctor if you have or have ever had kidney or liver disease.
- you should know that thioguanine may interfere with the normal menstrual cycle (period) in women and may stop sperm production in men. However, you should not assume that you cannot get pregnant or that you cannot get someone else pregnant. Women who are pregnant or breast-feeding should tell their doctors before they begin taking this medication. You should not plan to have children while receiving chemotherapy or for a while after treatments. (Talk to your doctor for further details.) Use a reliable method of birth control to prevent pregnancy. Thioguanine may harm the fetus.
- do not have any vaccinations (e.g., measles or flu shots) without talking to your doctor.

Side effects

Side effects from thioguanine are common and include:

- headache
- weakness or achiness
- darkening of the skin
- loss of appetite or weight

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Drug Information: Hydroxyurea

(Hydroxycarbamide)

URL of this page: http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682004.html

(hye drox ee yoor ee' a)

Brand name(s): Hydrea

IMPORTANT WARNING:

Hydroxyurea may cause severe, life-threatening side effects, including certain cancers. Talk to your doctor about the risks of using hydroxyurea for your condition.

About your treatment

Your doctor has ordered the drug hydroxyurea to help treat your illness. The drug in capsule form can be taken by mouth.

This medication is used to treat:

- melanoma
- chronic myelocytic leukemia
- ovarian cancer
- primary squamous cell carcinoma of the head and neck (excluding the lip)
- chronic myelogenous leukemia
- sickle cell anemia

This medication is sometimes prescribed for other uses; ask your doctor or pharmacist for more information.

Hydroxyurea is in a class of drugs known as urea derivatives; it slows or stops the growth of cancer cells in your body. In sickle cell anemia, hydroxyurea decreases the episodes of painful crisis by decreasing the sickling of red blood cells. The length of treatment depends on the types of drugs you are taking, how well your body responds to them, and the type of cancer you have.

Other uses for this medicine

Hydroxyurea also is used to treat polycythemia vera, psoriasis, hypereosinophilic syndrome, lung cancer, and a variety of other cancers. In addition, hydroxyurea has been used along with anti-infective and surgical therapy to treat chronic urinary tract infections caused by certain bacteria. Talk to your doctor about the possible risks of using this drug for your condition.

Precautions

Before taking hydroxyurea,

- tell your doctor and pharmacist if you are allergic to hydroxyurea or any other drugs.
- tell your doctor and pharmacist what prescription and nonprescription medications you are taking,

Table 1

Summary of kinds of cancer treated by antimetabolite chemotherapeutic products
(source: Medline Plus®)

Fluorouracil
Colon cancer
Rectum cancer
Breast cancer
Stomach cancer
Pancreas cancer
Others:
Cancer of the outside layer of the adrenal gland
Anus
Bladder
Cervix
Endometrium
Ovaries
Esophagus
Head and neck
Penis
Liver
Prostate
Skin
Vulva
Carcinoid tumors
Hepatoblastoma

Methotrexate
Cancer of the breast
Cancer of the head and neck
Lung cancer
Blood cancer
Bone cancer
Lymph cancer
Tumors in the uterus
Others:
Acute nonlymphocytic leukemia (cancer of the blood and lymph system)
Cancer of the Meninges
Bladder
Brain (lymphoma)
Cervix
Colon
Rectum
Esophagus
Ovaries
Pancreas

Penis
soft tissues of the body (muscles, connective tissue, vessels, fat)
Stomach
Hodgkin's lymphoma

Cytarabine
Cancers of the blood (leukemias)
Others:
Cancer of the lymph system
Cancer of the brain and spinal cord

Mercaptopurine
Leukemia

Thioguanine
Leukemia

Hydroxycarbamide /Hydroxyurea
Melanoma
Leukemia (chronic myelocytic leukemia and chronic myelogenous leukemia)
Cell carcinoma of the head, neck and cervix
Ovarian cancer

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